



## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **Food and Drug Administration**

#### **21 CFR Part 312**

**[Docket No. FDA-2019-N-2650]**

**RIN 0910-AH07**

### **Investigational New Drug Applications; Exemptions for Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic**

**AGENCY:** Food and Drug Administration, Health and Human Services (HHS).

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its regulations on investigational new drug applications (INDs) to exempt from the IND requirements certain clinical investigations of lawfully marketed foods for human consumption (including both conventional foods and dietary supplements) and cosmetics when the product is to be studied to evaluate its use as a drug. Under the proposal, clinical studies to evaluate a drug use of such products would not have to be conducted under an IND when, among other things, the study is not intended to support a drug development plan or a labeling change that would cause the lawfully marketed product to become an unlawfully marketed drug, and the study does not present a potential for significant risk to the health, safety, or welfare of subjects. Though exempt from the IND requirements, such investigations would still be subject to other regulations designed to protect the rights and safety of subjects, including requirements for informed consent and review by institutional review boards (IRBs). By exempting from the IND requirements certain clinical investigations of products lawfully marketed as a food or cosmetic, the proposed provisions are intended to reduce the regulatory burden of conducting such studies while retaining protections for human subjects.

**DATES:** Submit either electronic or written comments on the proposed rule by **[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

Submit comments on the collection of information under the Paperwork Reduction Act of 1995 by **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

**ADDRESSES:** You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The <https://www.regulations.gov> electronic filing system will accept electronic comments until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified as confidential, if submitted as detailed in “Instructions.”

*Instructions:* All submissions received must include the Docket No. FDA-2019-N-2650 for “Investigational New Drug Applications; Exemptions for Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as

“confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

Submit comments on the information collection under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at <https://www.reginfo.gov/public/do/PRAMain>. Find this particular information collection by selecting “Currently under Review - Open for Public Comments” or by using the search function. The title of this proposed collection is “Investigational New Drug Applications; Exemptions for Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic.”

**FOR FURTHER INFORMATION CONTACT:** *Regarding the proposed rule:* Brian Pendleton, Office of Policy, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-4614, [Brian.Pendleton@fda.hhs.gov](mailto:Brian.Pendleton@fda.hhs.gov).

*Regarding the information collection:* Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, [PRAStaff@fda.hhs.gov](mailto:PRAStaff@fda.hhs.gov).

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### I. Executive Summary

#### *A. Purpose of the Proposed Rule*

FDA is proposing to amend its IND regulations to exempt from the scope of the requirements certain clinical investigations studying drug uses of products that are lawfully marketed as foods for human consumption (including dietary supplements) or as cosmetics. The proposed rule would make it easier for sponsors and sponsor-investigators to conduct certain clinical investigations evaluating drug uses of foods or cosmetics while maintaining adequate safeguards for human subjects.

Currently, FDA regulations provide an exemption from the IND requirements for studies of lawfully marketed drug products that meet certain criteria, including that the study does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of these risks) associated with the use of the drug product. However, this exemption applies only to clinical investigations of *drug products* lawfully marketed in the United States, and therefore generally does not apply to clinical investigations of products marketed as foods for human consumption or as cosmetics.

FDA has exercised its enforcement discretion on a case-by-case basis and has not objected to certain clinical studies evaluating a drug use of a product lawfully marketed as a food or cosmetic being conducted without an IND, based on consideration of factors such as the purpose of the investigation and whether the study raises any concerns about the health, safety, and welfare of the subjects. This proposed rule would now establish exemptions from the IND requirements for drug studies of products lawfully marketed in the United States as a food or cosmetic when the studies meet criteria similar to those in the IND exemption for certain investigations of lawfully marketed drug products.

#### *B. Summary of the Major Provisions of the Proposed Rule*

The proposed rule would create two types of IND exemptions for drug studies of products lawfully marketed in the United States as foods or cosmetics. One exemption, the proposed “self-determined exemption,” would specify that a clinical investigation to evaluate a drug use of a product lawfully marketed in the United States as a conventional food for human

consumption, a dietary supplement, or a cosmetic is exempt from the IND requirements if certain conditions are met:

- The investigation is not intended to support a drug development plan for the product (including a future IND or application for marketing approval) or a labeling change that would cause the lawfully marketed product to become an unlawfully marketed drug;
- The investigation is conducted in compliance with the requirements for IRB review and informed consent;
- The investigation is conducted in compliance with the regulations governing promotion and commercial distribution of investigational drugs;
- The route of administration of the product in the investigation is the same as that of the lawfully marketed product; and
- The investigation meets certain criteria designed to protect the health, safety, and welfare of subjects.

Under this self-determined exemption, if a clinical investigation to evaluate a drug use of a product lawfully marketed in the United States as a food or cosmetic meets these criteria, the study would be exempt from the IND regulations. Provided the criteria are met, the study's sponsor (who may also be an investigator conducting the study, i.e., a sponsor-investigator) would not be required to submit an IND for the study or request that FDA exempt the study from the IND requirements (and we would not accept an IND for a study that we had determined was exempt).

Under the second IND exemption we propose to establish, the "FDA-determined exemption," the sponsor of a clinical investigation to evaluate a drug use of a product lawfully marketed in the United States as a food or cosmetic could ask the Agency to exempt the investigation from the IND requirements when the investigation meets the self-determined exemption criteria except for one or more of the subject health, safety, and welfare criteria, but the sponsor has concluded that the investigation nevertheless does not present a potential for

significant risk to subjects. To obtain such an exemption, the sponsor would submit a written request that includes information on the sponsor, the proposed investigation, and the product to be studied, as well as a description of why the investigation does not present a potential for significant risk to the health, safety, or welfare of subjects.

Upon receiving such a request for exemption from the IND requirements, FDA would evaluate any risks to subjects and would grant an exemption if we found that the investigation did not present a potential for significant risk (or decrease the acceptability of the risks) to the health, safety, or welfare of subjects. The proposal also would authorize FDA to exempt a study from the IND requirements on our own initiative if we determined, upon review of an IND for the study, that the study met the decision criteria for an FDA-determined exemption. The FDA-determined exemption proposal also states that we may revoke an exemption if we become aware of information suggesting that the investigation: (1) could present a potential for significant risk to the health, safety, or welfare of subjects or (2) does not meet any other eligibility requirement for the exemption.

Adopting these proposed IND exemptions would reduce the burden of conducting certain clinical investigations evaluating drug uses of products lawfully marketed as foods or cosmetics, as well as the Agency's burden of reviewing such studies, without eliminating requirements that help ensure the safety of subjects and the quality of data submitted in support of drug product approval.

### *C. Legal Authority*

We are issuing this proposed rule under FDA's authority to regulate drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHS Act).

### *D. Costs and Benefits*

Quantifiable benefits of this proposed rule are cost savings that come from reducing the burden of submitting INDs to FDA for clinical investigations to evaluate a drug use of a food or



cosmetic. The proposed rule would have a one-time, upfront cost for current and future sponsors and sponsor-investigators who would have to read the rule, if it is finalized. In addition, there would be costs to FDA associated with a new type of IND-related submission, a request for an FDA-determined exemption. The impact of reviewing this new submission is analyzed in section II.E of the Preliminary Economic Analysis of Impacts for this proposed rule, as a partial offset to the cost savings of the rule. Discounted over 10 years, the total net benefit of the rule is estimated to be \$33 million at a 3 percent discount rate and \$27 million at a 7 percent discount rate.

## II. Table of Abbreviations and Commonly Used Acronyms in This Document

| Abbreviation or Acronym | What It Means                                |
|-------------------------|--|
| ANDA                    | Abbreviated New Drug Application             |
| BLA                     | Biologics License Application                |
| CBER                    | Center for Biologics Evaluation and Research |
| CDER                    | Center for Drug Evaluation and Research      |
| FD&C Act                | Federal Food, Drug, and Cosmetic Act         |
| FDA                     | Food and Drug Administration                 |
| IND                     | Investigational New Drug Application         |
| IRB                     | Institutional Review Board                   |
| NDA                     | New Drug Application                         |
| OMB                     | Office of Management and Budget              |
| PHS Act                 | Public Health Service Act                    |

## III. Background

This proposed rule concerns the establishment of exemptions from the requirement to submit an IND before initiating certain clinical investigations evaluating drug uses of lawfully marketed food for human consumption (including both conventional foods and dietary supplements) and cosmetics. (We refer to these product categories collectively as “foods and cosmetics” in this document.) Following is a brief discussion of important terms used in this proposed rule, the applicability of the IND regulations in part 312 (21 CFR part 312) to clinical investigations of foods and cosmetics for use as drugs, and why the proposed exemptions are needed.

### *A. Definitions*

Before explaining the need for the proposed IND exemptions, we believe it is helpful to discuss several terms used in the proposed rule. Under § 312.3(a), the definitions and interpretations of terms contained in section 201 of the FD&C Act (21 U.S.C. 321) apply to those terms when used in the IND regulations. Therefore, the terms “food,” “dietary supplement,” “cosmetic,” and “drug” in the proposed exemptions are defined as they are in the FD&C Act.

“Food” is defined as articles used for food or drink for man or other animals, chewing gum, and articles used for components of any such article (section 201(f) of the FD&C Act). For purposes of the proposed exemptions, “food” does not include animal feed, pet food, or other food intended for consumption by animals other than humans. Examples of food include, but are not limited to, fruits, vegetables, fish, dairy products, eggs, raw agricultural commodities for use as food or as components of food, food ingredients, food additives (including substances that migrate into food from packaging and other articles that contact food), dietary supplements, dietary ingredients, infant formula, medical foods, beverages (including alcoholic beverages and bottled water), bakery goods, snack foods, candy, and canned foods.

“Dietary supplement” is defined, in part, as a product that is intended for ingestion to supplement the diet and that contains one or more dietary ingredients (section 201(ff) of the FD&C Act). Dietary ingredients include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet by increasing the total dietary intake, and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients (section 201(ff)(1) of the FD&C Act). Because dietary supplements are deemed to be food for most purposes, the term “food” includes dietary supplements (see section 201(ff) of the FD&C Act). Notably, however, dietary supplements are not deemed to be food for purposes of section 201(g) of the FD&C Act, which, as discussed below, defines “drug” for purposes of the FD&C Act (section 201(ff) of the FD&C Act).

The term “conventional food” is not defined in the FD&C Act or in FDA’s regulations. In this proposed rule, we use it to mean any food that is not a dietary supplement.

A “cosmetic” is an article (other than soap) intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, or an article intended for use as a component of any such article (section 201(i) of the FD&C Act).

The definition of “drug” includes, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals” (section 201(g)(1)(B) and (C) of the FD&C Act). This proposed rule applies only to products that are intended for investigational use as drugs in humans. A biological product subject to licensure under section 351 of the PHS Act (42 U.S.C. 262) fits within the drug definition under the FD&C Act. A “biological product” is a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings (section 351(i) of the PHS Act).

“Clinical investigation” is defined in the IND regulations as any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects (excluding use of a marketed drug in medical practice) (§ 312.3(b)). A “subject” is defined in the IND regulations as a human who participates in an investigation, either as a recipient of an investigational new drug or as a control; subjects may be healthy or have a disease (§ 312.3(b)).

A “sponsor” of a clinical investigation is an individual or entity (e.g., pharmaceutical or other company, governmental agency, academic institution, private organization, or other organization) who takes responsibility for and initiates the investigation (§ 312.3(b)). An “investigator” is an individual who actually conducts a clinical investigation (i.e., the

investigational drug is administered or dispensed to subjects under his or her immediate direction) (§ 312.3(b)). A person may be a “sponsor-investigator,” who is an individual who initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed (§ 312.3(b)). For simplicity, we refer to sponsors and sponsor-investigators collectively as “sponsors” in this document except in the proposed regulatory text.

### *B. Applicability of the IND Regulations*

The new drug provisions of the FD&C Act require that a person obtain approval of a new drug application (NDA) or abbreviated new drug application (ANDA) before introducing or delivering for introduction into interstate commerce a new drug (section 505(a) of the FD&C Act (21 U.S.C. 355(a))). Similarly, the PHS Act requires that a person obtain approval of a biologics license application (BLA) before introducing or delivering for introduction into interstate commerce a biological product (section 351(a) of the PHS Act). However, these approval requirements do not apply to a drug or biological product intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs, provided the sponsor of the study complies with the regulations in part 312 governing the use of investigational new drugs (section 505(i) of the FD&C Act). These regulations include provisions for the submission and FDA review of INDs (see, e.g., §§ 312.20, 312.40).

There are two primary objectives of IND review. First, IND review is designed to help ensure that the safety and rights of subjects of clinical investigations are protected. Second, as applied to Phase 2 and Phase 3 studies, IND review is intended to help ensure that the quality of data obtained from a clinical study is adequate to permit evaluation of the safety and effectiveness of a drug for which marketing approval is sought (§ 312.22(a)). Phase 2 studies are controlled clinical studies conducted to evaluate the effectiveness of a drug for a particular indication in patients with the disease or condition under study or to determine the short-term side effects and risks associated with the drug (§ 312.21(b)). Phase 3 studies are expanded

controlled and uncontrolled trials performed after preliminary evidence suggesting a drug's effectiveness has been obtained; they are intended to gather additional information about effectiveness and safety needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling (§ 312.21(c)). Sponsor compliance with IND requirements (such as for the content and format of INDs (§ 312.23), safety reports (§ 312.32), annual progress reports (§ 312.33), and monitoring of investigations (e.g., §§ 312.50, 312.53, and 312.56)) and FDA review of the content of INDs, protocol amendments (§ 312.30), safety reports, annual progress reports, and other IND-related information help ensure that subjects are adequately protected and that sponsors may rely on data from investigations to support applications for approval.

Section 312.2(a) states that the IND requirements apply to all clinical investigations of products that are subject to section 505 of the FD&C Act (which includes the new drug approval requirement) or the biological product licensing provisions of the PHS Act. However, there are a few exemptions from the IND requirements set forth in § 312.2(b). For the purposes of the proposed rule, the most significant of these exemptions concerns certain investigations of drug products lawfully marketed in the United States. Under § 312.2(b)(1), a clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the IND regulations if all the following apply:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor to support any other significant change in the labeling for the drug;
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

- The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug;
- The investigation is conducted in compliance with the requirements for review by an IRB in part 56 (21 CFR part 56) and the requirements for informed consent in part 50 (21 CFR part 50); and
- The investigation is conducted in compliance with the requirements in § 312.7, which govern promotion and commercial distribution of investigational new drugs, among other things.

Section 312.2(b)(1) was created during the revision of the IND regulations in the 1980s (“IND Rewrite”) because it became clear that physicians, especially those affiliated with academic institutions, sought to conduct clinical investigations using marketed drugs, either to investigate new uses or to use the drug as a research tool to explore biological phenomena or disease processes (48 FR 26720, June 9, 1983). Although such clinical investigations are subject to section 505(i) of the FD&C Act, FDA reevaluated the utility of reviewing these INDs and concluded that our review of certain categories of INDs was not necessary to ensure the protection of study subjects. Accordingly, in the final rule adopting the IND Rewrite, we exempted from the IND requirements clinical investigations of lawfully marketed drugs that meet specific criteria designed to help ensure that exempted investigations do not expose subjects to new risks (52 FR 8798 at 8832, March 19, 1987) (codified in § 312.2(b)(1)). Under § 312.2(b)(1)(iv), investigators conducting exempt studies are still required to conform to all ethical principles applicable to the conduct of clinical investigations, including the statutory requirement for informed consent (section 505(i)(4) of the FD&C Act). Thus, a study’s exemption is conditioned on a sponsor complying with the requirements for informed consent set forth in part 50 as well as the requirements for review and approval by an IRB set forth in part 56. Finally, the sponsor is prohibited from test marketing or commercially distributing the

product and from promoting the product for its investigational use (see §§ 312.2(b)(1)(v) and 312.7).

*C. Guidance on Whether Clinical Investigations Can Be Conducted Without an IND*

To address questions about the applicability of the IND regulations to certain types of clinical investigations, in the *Federal Register* of October 14, 2010, we issued a notice of availability (75 FR 63189) of a draft guidance entitled “Guidance for Industry: Investigational New Drug Applications (INDs)--Determining Whether Human Research Studies Can Be Conducted Without an IND” (“2010 Draft IND Guidance”). In addition to explaining when the FD&C Act and FDA regulations require an IND to be submitted, the draft guidance described the types of clinical investigations that are exempt by regulation from the IND requirements and addressed a range of issues that commonly arise in inquiries to FDA about the application of those requirements.

On September 10, 2013, we issued a notice of availability (78 FR 55262) of the final version of that draft guidance, entitled “Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards (IRBs) on Investigational New Drug Applications--Determining Whether Human Research Studies Can Be Conducted Without an IND” (“2013 IND Guidance” (Ref. 1)). Like the draft guidance (2010 Draft IND Guidance), the final guidance notes that a “drug” is not limited to articles intended to have a therapeutic purpose (i.e., to diagnose, cure, mitigate, treat, or prevent a disease), but also includes articles (other than food) intended to affect the structure or function of the body. For example, an article administered to healthy individuals to prevent pregnancy or treat male pattern baldness is a drug. The 2013 IND Guidance further explained that the drug definition also includes articles used for research purposes in healthy subjects to blunt or provoke a physiologic response or study the mechanism of action or metabolism of a drug (Ref. 1 at 3).

The final guidance also explains the application of the IND regulations to studies of ingredients or products marketed as foods or cosmetics. The guidance explains that a clinical

investigation assessing the use of a conventional food for a therapeutic purpose (e.g., to relieve symptoms of Crohn's disease) would be a study to evaluate a drug use of the food and would therefore require an IND (Ref. 1 at 12-13; see also section 201(g)(1)(B) of the FD&C Act). However, a clinical study designed to evaluate the safety or tolerability of a food ingredient when ingested as food (i.e., primarily for its taste, aroma, or nutritive value) would not be a study to evaluate a drug use, so an IND would not be required (Ref. 1 at 13-14; see also section 201(g)(1)(C) of the FD&C Act and *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir. 1983)).

Regarding dietary supplements, the final guidance explains that a dietary supplement intended only to affect the structure or function of the body and not intended for a therapeutic purpose is not a drug (Ref. 1 at 12; see also sections 201(g)(1) and 403(r)(6) of the FD&C Act (21 U.S.C. 321(g)(1) and 343(r)(6)). Therefore, an IND is not required for a clinical investigation intended only to evaluate a dietary supplement's effect on the structure or function of the body. However, if a clinical investigation is intended to evaluate a dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required.

The final guidance explains that clinical investigations of ingredients or products marketed as cosmetics require an IND if the ingredient is being studied for use to affect the structure or function of the body or for a therapeutic purpose (Ref. 1 at 11). This is because section 201(g)(1)(B) and (C) of the FD&C Act defines as drugs both articles (other than food) intended to affect the structure or function of the body and articles intended to diagnose, cure, mitigate, treat, or prevent a disease.

Because FDA received multiple comments asking for further opportunity to comment on portions of the final guidance (sections VI.C and VI.D) addressing the applicability of the IND regulations to clinical investigations evaluating drug uses of foods (including dietary supplements) or cosmetics, on February 6, 2014, we reopened the comment period on those sections of the guidance (79 FR 7204). These comments raised questions about application of the IND requirements to certain clinical studies of conventional foods, dietary supplements, and



cosmetics being investigated for uses covered by the drug definition in section 201(g)(1)(B) or (C) of the FD&C Act.

On October 30, 2015, we issued a notice of administrative stay of action staying parts of the final guidance to allow for further consideration of issues raised by comments received following the reopening of the comment period (80 FR 66907). Specifically, we stayed portions of section VI.D.2, “Conventional Food” (concerning clinical studies to evaluate non-nutritional effects on the structure or function of the body), and all of section VI.D.3, “Studies Intended to Support a Health Claim” (except as to studies intended to evaluate whether a food substance reduces the risk of a disease in individuals less than 12 months old, those with altered immune systems, and those with serious or life-threatening medical conditions). The stayed portion of section VI.D.2 states that under the applicable regulations, a clinical investigation intended only to evaluate the nutritional effects of a food (including medical foods) would not require an IND, but an investigation intended to evaluate other effects of a food on the structure or function of the body would require an IND. Section VI.D.3 (stayed except as to studies that include subjects in the three medically vulnerable categories previously described) states that under the applicable regulations, a clinical study designed to evaluate the relationship between a food substance and a disease, and intended to provide support for a health claim about reducing the risk of the disease, must be conducted under an IND, unless the substance-disease relationship being studied is already the subject of an authorized health claim under section 403(r)(1)(B) and (r)(3) of the FD&C Act (for a conventional food) or section 403(r)(1)(B) and (r)(5)(D) (for a dietary supplement). The notice announcing the administrative stay of portions of the final guidance states that we do not intend to enforce the IND requirement for studies in the stayed categories while the stay is in effect (80 FR 66907 at 66908 to 66909).

As previously stated, some clinical investigations of products marketed as foods and cosmetics are included among the types of studies that are required by the FD&C Act and FDA regulations to be conducted under an IND. Under the proposed rule, some of these clinical

investigations would be exempt from the IND requirements if they meet the proposed exemption criteria discussed in section V of this document. At the completion of this rulemaking, we anticipate taking action to resolve related issues in the final guidance, including the stayed portions of the guidance.

#### *D. Need for the Regulation*

In recent years, FDA has received inquiries about many clinical investigations evaluating a drug use of an article marketed as a food or cosmetic. Examples of such articles include conventional foods such as potatoes and dried fruit; dietary supplements such as soy isoflavones, vitamins, and green tea extract; and cosmetics such as lavender oil and hydroquinone (which is a cosmetic when used as a fragrance ingredient or hair colorant, but a drug when used to bleach the skin by decreasing the formation of melanin). Products in these categories have been studied to evaluate their use in treating, mitigating, curing, or preventing diseases such as asthma, diabetes, arthritis, gastrointestinal disorders, depression, cardiovascular disease, and cancer.

In some cases, the sponsor of a clinical investigation of a food or cosmetic--often, the manufacturer of the product--seeks to study the product for use in treating, mitigating, curing, or preventing a disease because the sponsor hopes to develop and obtain marketing approval of the product as a drug, has a financial relationship with an entity that hopes to obtain such marketing approval, or wishes to market the product for disease treatment or prevention without seeking approval for it as a new drug. For example, the manufacturer of a dietary supplement marketed with a claim that the product “supports digestive health” might wish to sponsor a clinical investigation designed to evaluate the product’s ability to treat a digestive disorder. However, in other cases, a person or institution may have a purely scientific or medical interest in studying a conventional food, dietary supplement, or cosmetic for a drug use. For example, physicians and other researchers in hospitals and universities often explore potentially novel mechanisms of action of a food or cosmetic to understand whether such a product could have an effect on an aspect of a disease or medical condition. In many cases, such researchers have no intent to seek

approval of the product as a drug or market it unlawfully for disease treatment or prevention without such approval, no financial interest in the product, and no research funding or other financial support from the product's manufacturer or other potential sponsors of an application for drug marketing approval.

Review divisions in the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) frequently receive inquiries from study sponsors and investigators about whether the IND requirements apply to a planned study to evaluate a drug use of a food or cosmetic. In some cases, the sponsor asserts that the study is exempt from the IND requirements under § 312.2(b)(1). However, most of these studies are not eligible for the exemption in § 312.2(b)(1) because the study is not a clinical investigation of a drug product that is lawfully marketed in the United States. Nevertheless, in some cases, the Agency has concluded that it is not necessary or desirable to apply the IND requirements to a proposed drug study of a food or cosmetic because the study poses minimal risks to subjects and is not intended to be used in support of a drug marketing application, drug development plan, or labeling change that would cause the lawfully marketed food or cosmetic to become an unlawfully marketed drug. In such cases, we have exercised enforcement discretion regarding the submission of an IND for the study and the IND reporting requirements (e.g., study progress and safety reports). Sponsors of such studies must still comply with FDA regulations on the protection of human subjects and IRB review (parts 50 and 56, respectively), along with the IND regulation regarding promotion and commercial distribution of investigational drugs (§ 312.7), and they are expected to notify us of any changes to the study protocol that could affect subjects' safety.

We believe that establishing IND exemptions for certain clinical investigations of drug uses of foods and cosmetics based on the principles behind the adoption of § 312.2(b)(1) would reduce regulatory and resource burdens on sponsors, investigators, and the Agency in circumstances when application of the IND requirements is not needed to ensure adequate

protection of human subjects. Many of the proposed clinical investigations of foods and cosmetics that we have considered in recent years would have been eligible for either the proposed self-determined exemption or FDA-determined exemption. Codifying IND exemptions for investigations of drug uses of foods and cosmetics that meet certain criteria similar to the eligibility criteria for exempting studies of lawfully marketed drug products under § 312.2(b)(1) could result in reduced research costs for sponsors, fewer inquiries submitted to CBER and CDER review divisions, and greater numbers of clinical trials (because FDA consultation would not be needed for the self-determined exemption), without compromising the health, safety, or welfare of subjects or undermining the quality of data needed to support drug marketing approval.

#### IV. Legal Authority

This proposed rule would exempt from the IND regulations in part 312 certain clinical investigations evaluating drug uses of products lawfully marketed in the United States as foods (including dietary supplements) or cosmetics. These exemptions would track the exemption already provided in § 312.2(b)(1) for certain clinical investigations of lawfully marketed drugs.

Under section 701(a) of the FD&C Act (21 U.S.C. 371(a)), the Agency is empowered to issue regulations for the efficient enforcement of that statute. FDA's primary objective in reviewing an IND is to assure the rights, safety, and welfare of subjects (see 48 FR 26720 at 26725 and § 312.60), with a secondary objective of helping to ensure that the quality of data obtained from a Phase 2 or Phase 3 clinical study is adequate to permit evaluation of the drug's safety and effectiveness (§ 312.22(a)). Like any other clinical investigation where the intended use to be studied brings the investigational product within the drug definition, clinical investigations evaluating drug uses of foods and cosmetics are subject to section 505(i) of the FD&C Act. However, after reevaluating the utility of requiring such clinical investigations to be conducted under an IND, FDA finds that these investigations are remarkably diverse with respect to the composition and risk profile of the products studied, the health of the study subjects, and

the nature of the study procedures (e.g., invasive vs. non-invasive testing). Accordingly, we have drafted subject protection and study purpose criteria in an attempt to define categories of low-risk clinical investigations that can be exempted from the IND requirements without compromising human subject protection or the quality of data used to support drug marketing applications. FDA tentatively concludes that, for clinical investigations that meet the proposed criteria, review of an IND is not necessary for subject protection and would be an inefficient use of sponsor and Agency resources. Therefore, under our authority to issue regulations for the efficient enforcement of the FD&C Act, we are proposing to exempt clinical investigations that meet the proposed criteria from the IND requirements.

We are also issuing this proposed rule under FDA's authority to regulate unapproved new drug products under the FD&C Act (see sections 201, 301, 501, 502, 503, 505, 561, and 701) (21 U.S.C. 321, 331, 351, 352, 353, 355, 360bb, and 371) and section 351 of the PHS Act.

## V. Description of the Proposed Rule

We are proposing to amend the IND regulations to establish two exemptions for clinical investigations evaluating a drug use of a food or cosmetic. Under the first exemption provision, a clinical investigation to evaluate a drug use of a food or cosmetic would be exempt from the IND requirements if certain criteria were met regarding: (1) the intent of the investigation; (2) compliance with requirements and restrictions regarding institutional review, informed consent, and promotion and commercial distribution of investigational drugs; (3) the route of administration of the product as used in the investigation; and (4) protection of subjects' health, safety, and welfare. Because a sponsor would self-determine whether the investigation met the criteria to be conducted without an IND, we refer to this exemption as the "self-determined exemption."

Under the second proposed exemption, a sponsor of an investigation that did not meet one or more of the self-determined exemption's health, safety, and welfare criteria, but did meet all the other criteria for the self-determined exemption, could submit to us a written request for

exemption if the sponsor concluded that the study nevertheless did not present a potential for significant risk to the health, safety, or welfare of subjects. Under this “FDA-determined exemption,” we would grant an exemption if we found that the investigation did not present a potential for significant risk. In addition to authorizing the Agency to grant an FDA-determined exemption upon the request of a sponsor, the proposed rule would allow FDA to exempt a study on our own initiative if we determined, upon review of an IND that had been submitted for the study, that the study met the decision criteria for an FDA-determined exemption. The proposed rule would also permit us to revoke an exemption we had granted if we subsequently became aware of information suggesting that the study presented a potential for significant risk to the health, safety, or welfare of subjects, or that the study did not meet any of the other requirements for the exemption.

The proposed self-determined and FDA-determined exemptions (including the FDA-initiated exemption) would be set forth in proposed § 312.2(b)(4) and (5), respectively, with existing exemptions and related provisions in current § 312.2(b)(4) through (6) to be renumbered accordingly. In addition, we propose to amend current § 312.2(b)(4), which states that we will not accept an IND for investigations exempt under § 312.2(b)(1), to specify that we also would not accept an IND for investigations exempt under proposed § 312.2(b)(4) and (5).

The following paragraphs describe the proposed self-determined and FDA-determined exemption provisions and other proposed changes to § 312.2(b).

*A. Self-Determined Exemption (Proposed § 312.2(b)(4))*

Under proposed § 312.2(b)(4), a clinical investigation to evaluate a drug use of a product lawfully marketed in the United States as a food intended for human consumption (including as a conventional food or dietary supplement) or as a cosmetic would be exempt from the IND requirements if the following criteria are met:

- The investigation is not intended to support a drug development plan for the product, including a future IND or application for marketing approval (an application under

section 505 of the FD&C Act or section 351 of the PHS Act), or to support a change in the labeling of the lawfully marketed product that would cause it to become an unlawfully marketed drug;

- The investigation is conducted in compliance with the requirements for institutional review in part 56 and the requirements for informed consent in part 50;
- The investigation is conducted in compliance with the requirements of § 312.7;
- The route of administration of the product in the investigation is the same as that of the lawfully marketed product; and
- The investigation meets the following criteria relating to the health, safety, and welfare of study subjects:
  - The investigation does not include subjects who are less than 12 months of age or subjects who are pregnant or lactating;
  - The investigation does not include subjects with a compromised immune system or a serious or life-threatening disease or condition;
  - The investigation does not restrict subjects from continuing with treatments or therapies prescribed or recommended by a healthcare provider;
  - The investigation does not involve any procedures that would increase the risks (or decrease the acceptability of the risks) to subjects beyond what they would ordinarily encounter during routine physical or psychological examinations or standard of care procedures to treat their medical condition;
  - The product is being used in the investigation consistent with its labeled conditions of use or, in the absence of labeled conditions of use, consistent with its ordinary conditions of use (e.g., same dose range and total daily intake, same formulation, same duration of use); and
  - During the investigation, subjects are not taking and will not be treated with any other product(s) that would significantly increase the risks (or decrease the

acceptability of the risks) they will encounter in the investigation (e.g., because of drug interactions).

The following paragraphs discuss the scope and criteria of the proposed self-determined exemption in more detail.

#### 1. Products Lawfully Marketed in the United States as Foods or Cosmetics

The self-determined exemption would apply to studies of products that are lawfully marketed in the United States as foods intended for human consumption (including as a dietary supplement) or as cosmetics (proposed § 312.2(b)(4)). For purposes of the proposed self-determined exemption, “lawfully marketed” means the product is marketed in the United States as a food or cosmetic consistent with the FD&C Act and any applicable FDA regulations.

#### 2. Clinical Investigation to Evaluate a Drug Use

The proposed self-determined exemption would apply to clinical investigations evaluating a food or cosmetic for use as a drug (proposed § 312.2(b)(4)). The intended use of a product determines whether the product fits within the definition of a “drug” under the FD&C Act (see section III.C of this document).

#### 3. Not Intended to Support a Drug Development Plan or Marketing for Use as a Drug

The proposed self-determined exemption would not apply to a clinical investigation intended to support a drug development plan for a food or cosmetic, including a future IND or marketing approval application, or to support a change in the labeling of the food or cosmetic that would cause the product to become an unlawfully marketed drug (proposed § 312.2(b)(4)(i)). For example, this means that if the investigation were intended to support a future IND for a clinical trial investigating a drug use of the product, or a future NDA or BLA for the product, the investigation would not be eligible for the exemption.

As previously noted, the IND exemption for clinical investigations of lawfully marketed drug products in existing § 312.2(b)(1) does not apply to a study intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support



any other significant change in a drug’s labeling. In proposing this criterion in the 1983 IND Rewrite, FDA stated that the criterion was “aimed at helping ensure that investigations intended to be submitted to FDA for labeling or advertising changes are adequate in design to serve that purpose” (48 FR 26720 at 26733). We further stated that this is the “same reason the agency evaluates the design of Phase 2 and Phase 3 studies,” noting that this review “adds considerable efficacy to the drug development process” (48 FR 26720 at 26733). Similarly, if a clinical investigation of a food or cosmetic is intended to support a drug development plan for that product, the investigation must be conducted under an IND to help ensure that the quality of the scientific evaluation of the product is adequate to permit an evaluation of the product’s effectiveness and safety when used as a drug, including whether data from the investigation can be used to support approval of the product as a drug (see § 312.22(a)).

The self-determined exemption also would not apply if the sponsor of the clinical investigation intended to use the study to support marketing of the food or cosmetic for a use that caused the product to be an unlawfully marketed drug. For example, if a sponsor sought to study a dietary supplement to support marketing it for a disease treatment use (rather than for a structure or function use), the study would not be eligible for the self-determined exemption. Similarly, the exemption would not apply to a study intended to support the addition of a drug claim to the label of a conventional food or a cosmetic.

#### 4. Conducted in Compliance with Part 56 and Informed Consent Requirements of Part 50

To be eligible for the proposed self-determined exemption, the study must also be conducted in compliance with the IRB requirements in part 56 and the informed consent requirements in part 50 (proposed § 312.2(b)(4)(ii)). This criterion would mirror the provision in § 312.2(b)(1)(iv) that requires compliance with the IRB and informed consent requirements as a condition of eligibility for the IND exemption for certain studies of drug products lawfully marketed in the United States.

#### 5. Conducted in Compliance with § 312.7

Another eligibility criterion for the proposed self-determined exemption matching a criterion for the exemption for lawfully marketed drugs is the proposed requirement that the investigation be conducted in compliance with § 312.7 (proposed § 312.2(b)(4)(iii)). Among other things, § 312.7 prohibits commercially distributing or test marketing an investigational new drug, as well as representing in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation.

#### 6. Same Route of Administration as Lawfully Marketed Food or Cosmetic

Another eligibility criterion for the proposed self-determined exemption that is based on a criterion for the exemption for lawfully marketed drugs is the requirement that the route of administration of the product in the investigation be the same as that of the lawfully marketed product (proposed § 312.2(b)(4)(iv)). For example, a clinical investigation of a product lawfully marketed as a dietary supplement for oral ingestion would not qualify for the exemption if the product would be administered topically or transmucosally (i.e., sublingually, buccally, or intranasally) when used as a drug in the investigation. Similarly, a clinical investigation of a product lawfully marketed as a cosmetic applied to the skin would not qualify for the exemption if the product would be administered subcutaneously, intravenously, or intramuscularly when used as a drug in the investigation. This requirement would ensure that the self-determined and FDA-determined exemptions are limited to investigations evaluating drug uses of foods and cosmetics when the investigational products are administered in the same way as the marketed products, thereby avoiding potential safety risks posed by atypical routes of administration (e.g., products marketed as dietary supplements being studied as injectable drugs).

#### 7. Criteria to Help Ensure Health, Safety, and Welfare of Subjects

The proposed self-determined exemption includes several eligibility criteria designed to protect the health, safety, and welfare of study subjects (proposed § 312.2(b)(4)(v)). These criteria, discussed in the following paragraphs, are intended to serve the same purpose as the requirement under the lawfully marketed drug exemption that the investigation not involve a

dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug product (§ 312.2(b)(1)(iii)). Because of age-dependent development, immune system impairment, or other physiological differences, certain populations (described in the following paragraphs) may have the potential for a higher degree of risk or different risks compared to the general population. The proposed health, safety, and welfare criteria are especially important because, under the self-determined exemption, FDA would not have an opportunity to evaluate potential safety concerns before a proposed study begins.

- a. No subjects less than 12 months of age or who are pregnant or lactating.

To be eligible for the self-determined exemption, a proposed study could not involve subjects less than 12 months of age or subjects who are pregnant or lactating (proposed § 312.2(b)(4)(v)(A)). We are proposing this criterion because foods and cosmetics that would not pose a safety concern in the general population may not be safe for study in these vulnerable populations. For example, a study to evaluate use of honey or a honey-containing product to prevent diarrhea in subjects less than 12 months of age would pose a risk of botulism if *Clostridium botulinum* spores were present in the honey. These medically vulnerable populations pose special safety concerns typically requiring that an investigation be conducted under the protections afforded by an IND (although it is possible that a sponsor could show, in a request for an FDA-determined exemption, that a particular investigation involving such a population does not present a potential for significant risk to subjects' health, safety, or welfare).

- b. No subjects with a compromised immune system or a serious or life-threatening disease or condition.

The self-determined exemption would not apply if a proposed study included subjects with a compromised immune system or a serious or life-threatening disease or condition (proposed § 312.2(b)(4)(v)(B)). A person with an immune system impaired or weakened by disease (e.g., diabetes, cancer), malnutrition, or drugs (e.g., chemotherapy) may be unable to

fight off an infection. For example, a study to evaluate use of a probiotic dietary supplement in adult subjects to prevent nausea associated with chemotherapy might pose a risk of mucormycosis due to fungal contamination of the probiotic.

A “serious” disease or condition is one that is associated with persistent or recurrent morbidity (a diseased condition or state) that has substantial impact on day-to-day functioning; the morbidity need not be irreversible to be “serious” if it is persistent or recurrent (see § 312.300(b)). FDA considers a disease or condition to be “life-threatening” if: (1) the likelihood of death is high unless the course of the disease is interrupted or (2) the disease or condition has a potentially fatal outcome (see § 312.81(a)). For example, a study to evaluate high doses of a vitamin in adults with insulin-dependent diabetes might pose risks of worsening kidney or heart function. Similarly, a study of the herbal product valerian, which potentiates the effects of alcohol, could be dangerous in adults with alcohol use disorder. Because the potential risks to subjects would generally warrant that the investigation be conducted under the IND requirements and their protections for subjects who have a serious or life-threatening disease, a study of a food or cosmetic to treat even a non-serious disease would not be eligible for the self-determined exemption if the study included such subjects.

c. Continuing treatments or therapies prescribed or recommended by a healthcare provider.

To be eligible for the self-determined exemption, the investigation could not restrict the subjects of the study from continuing with any treatment or therapy prescribed or recommended for them by a healthcare provider (proposed § 312.2(b)(4)(v)(C)). Healthcare providers could include, for example, physicians, physician assistants, dentists, physical therapists, and nurses. Being unable to continue a course of treatment or therapy that one’s physician, therapist, or other healthcare provider has prescribed or recommended could significantly increase risks for a subject; therefore, an investigation in which this might occur usually warrants the protections of an IND.

d. No study procedures that would increase the risks to subjects beyond what are ordinarily encountered.

Another proposed eligibility criterion for the self-determined exemption is that the investigation not involve any procedures that would increase the risks (or decrease the acceptability of the risks) to subjects beyond what they would ordinarily encounter during a routine physical or psychological examination or standard of care procedures to treat their medical condition (proposed § 312.2(b)(4)(v)(D)). For example, using an invasive technique such as a biopsy to evaluate a study endpoint in subjects who ordinarily would be monitored with routine blood tests might increase risks to the subjects. Studies with the potential to expose subjects to greater risk than they would normally encounter in the course of their clinical care should not be conducted without an IND unless the sponsor can show (in a request for an FDA-determined exemption) that no such increase in risk will occur.

e. Product used consistent with labeled or ordinary conditions of use.

Another proposed criterion for eligibility for the self-determined exemption is that the product would have to be used in the investigation consistent with its labeled conditions of use when lawfully marketed as a food or cosmetic (§ 312.2(b)(4)(v)(E)). In the absence of labeled conditions of use, the product would have to be used consistent with its ordinary conditions of use as a lawfully marketed food or cosmetic (e.g., same dose range and total daily intake, same formulation, same duration of use). This eligibility criterion would help ensure that a clinical investigation not conducted under an IND does not pose significant risks to subjects due to atypical use of the product.

For a product that does not have labeled conditions of use, the “ordinary” conditions of use would be those found in a regulation prescribing conditions of safe use (e.g., a food additive or color additive regulation), if such a regulation exists. For products that do not have a regulation prescribing conditions of safe use (such as dietary supplements, cosmetics, and most conventional foods), the “ordinary” conditions of use could be those recommended in, for

example, the following: guidelines issued by the Department of Health and Human Services, one of its components (such as the National Institutes of Health), or another Federal Agency; recommendations from a division of the National Academy of Sciences or the National Academy of Medicine; publicly available websites of medical societies and professional associations; and guidelines recognized by a professional medical society or nutrition association. For example, although vitamin D products may lack directions for use in children, the American Academy of Pediatrics has issued recommendations on vitamin D supplementation in children.

f. No other product taken by or used to treat subjects during the investigation would significantly increase the risks (or decrease acceptability of the risks) encountered in the investigation.

The last proposed eligibility criterion for the self-determined exemption would limit the exemption to clinical investigations in which the subjects are not taking and will not be treated with any other product that would significantly increase the risks (or decrease the acceptability of the risks) they will encounter in the investigation (proposed § 312.2(b)(4)(v)(F)). For example, drinking grapefruit juice can increase the bioavailability of blood pressure-lowering drugs in the body, and taking the herb ginseng can enhance the bleeding effects of heparin, aspirin, and nonsteroidal anti-inflammatory drugs such as ibuprofen (Ref. 2). Because administering a food or cosmetic as an investigational drug to study subjects who are taking or are being treated with another FDA-regulated product could significantly increase risks to these subjects, such an investigation should not be conducted without an IND unless the sponsor can show (in a request for an FDA-determined exemption) that no such increase in risk will occur.

## 8. Application of the Self-Determined Exemption

Under the proposed self-determined exemption, a sponsor would not be required to submit a request to FDA for exemption from the IND requirements. (Moreover, as discussed in section V.C of this document, we would not accept an IND for an investigation that is exempt from the IND requirements under the self-determined exemption.) If a sponsor determines that

its proposed study meets the eligibility criteria for the exemption, the sponsor may proceed with the study without having to submit an IND.

If the sponsor later revises the protocol or otherwise changes the study so that it no longer meets the eligibility criteria for the self-determined exemption, the sponsor would have to submit an IND for the study or a request for an FDA-determined exemption under proposed § 312.2(b)(5). In addition, if FDA becomes aware (such as during an IRB inspection or through communications from the sponsor, an investigator, a subject, or the IRB) that a study conducted without an IND in reliance on the self-determined exemption is ineligible for the exemption, we may issue an untitled letter or warning letter to the study sponsor and, if necessary, take appropriate enforcement action, such as seeking an injunction.

*B. FDA-Determined Exemption (Proposed § 312.2(b)(5))*

Some proposed investigations to evaluate a drug use of a food or cosmetic may not meet all the safety-related eligibility criteria for the self-determined exemption, but FDA still might conclude, under appropriate circumstances, that the study does not pose a significant risk to the health, safety, or welfare of subjects. For example, even in an investigation that included subjects with a serious disease, if the product to be studied and the study procedures were low risk, we might conclude, depending on other subject characteristics and the intended use of the investigational product, that the study did not present a potential for significant risk that would necessitate conducting the study under an IND. For example, we might conclude that an investigation evaluating the use of beetroot juice to mitigate, treat, or prevent signs and symptoms of chronic kidney disease did not present a potential for significant risk to subjects because, among other factors, subjects would continue to receive standard of care treatment for their disease. Therefore, we propose to establish an “FDA-determined exemption” under which a sponsor of a study that does not meet one or more of the subject health, safety, and welfare criteria for the self-determined exemption could request an IND exemption from FDA.

1. Request for an Exemption

Under the FDA-determined exemption, a sponsor could request that we exempt from the IND requirements a clinical investigation to evaluate a drug use of a product lawfully marketed in the United States as a food or cosmetic when the investigation satisfies the requirements of the self-determined exemption except for one or more of the criteria related to the health, safety, or welfare of subjects (in proposed § 312.2(b)(4)(v)), but the sponsor has concluded that the study nevertheless does not present a potential for significant risk to subjects' health, safety, or welfare (proposed § 312.2(b)(5)(i)). The request would have to be in writing and would be required to contain the following information.

a. Study protocol or protocol summary.

A request for an FDA-determined IND exemption for a drug study of a food or cosmetic would be required to include a copy of the study protocol or a detailed protocol summary that includes, at a minimum, the following: the study design and duration; proposed endpoints; the study population, including inclusion and exclusion criteria for subjects; a description of the specific product to be studied as an investigational drug, including ingredients, composition, and any labeling; the dosage form, dosing regimen, and route of administration of the investigational drug; the study procedures (including safety monitoring procedures); and planned modifications to the protocol in the event of adverse events (proposed § 312.2(b)(5)(i)(A)). This information about the proposed study is necessary to give FDA an adequate context in which to assess the potential risks to subjects and decide whether to exempt the study from the IND requirements.

b. Names of manufacturer and source of product to be studied.

A request for exemption would have to include the names of the manufacturer and the entity that is the source of the specific product to be studied in the investigation (proposed § 312.2(b)(5)(i)(B)). In cases where the product to be studied will be provided directly by the manufacturer, the manufacturer and source of the investigational product will be the same. However, in some cases, the investigational product might be obtained from someone other than the manufacturer, such as a distributor.



For foods not in package form and not labeled with the name of the manufacturer, the exemption request would only have to provide the source of the product.

c. Name and form of lawfully marketed food or cosmetic product; labeling.

A request for exemption would have to include the name (if different from the name of the product to be studied in the investigation) and form (e.g., conventional food, liquid, tablet, lotion) of the lawfully marketed food or cosmetic product, and a copy of the product labeling (proposed § 312.2(b)(5)(i)(C)). If the product's labeling does not identify its ingredients, the sponsor would also be required to provide a description of the composition of the product.

d. Source(s) of funding for the investigation.

A request for exemption would have to include the source(s) of funding for the investigation (proposed § 312.2(b)(5)(i)(D)). This information is needed to help ensure that an investigation is not intended to support a drug development plan for the product being studied, which is a requirement for eligibility for the FDA-determined exemption. For example, if an investigation is funded by the manufacturer of the investigational product or by a trade association representing the interests of firms that manufacture that type of product, we would consider the funding source as a factor in determining whether an investigation is intended to support a drug development plan for the product.

e. Information about the sponsor.

A request for exemption would have to include the name, address, telephone number, email address, and contact name for the sponsor (proposed § 312.2(b)(5)(i)(E)). This information will, among other things, enable us to contact the sponsor if we have any questions and to provide our response to the request.

f. Description of why the investigation does not present a potential for significant risk to the health, safety, or welfare of subjects.

A request for exemption would have to include a brief description of why the investigation does not present a potential for significant risk to the health, safety, or welfare of

subjects, including, where relevant, the following information regarding the subject health, safety, and welfare eligibility criteria set out in the self-determined exemption (proposed § 312.2(b)(5)(i)(F)):

- If the proposed investigation includes subjects who are less than 12 months of age or subjects who are pregnant or lactating, the exemption request would have to include information to demonstrate that the use of the investigational product does not present a potential for significant risk to the health, safety, or welfare of these subjects (proposed § 312.2(b)(5)(i)(F)(1)).
- If the investigation includes subjects with a compromised immune system or a serious or life-threatening disease or condition, the exemption request would have to include information to demonstrate that the use of the investigational product does not present a potential for significant risk to the health, safety, or welfare of these subjects (proposed § 312.2(b)(5)(i)(F)(2));
- If participation in the investigation will preclude subjects from continuing with a treatment or therapy prescribed or recommended for them by a healthcare provider (e.g., if some subjects randomized to the investigational product or placebo will be instructed to discontinue their current treatment), the exemption request would have to include an explanation of why this restriction would not present a potential for significant risk to the health, safety, or welfare of these subjects (proposed § 312.2(b)(5)(i)(F)(3));
- If the subjects in the investigation will undergo any procedures during the investigation that would expose them to more risk than they would ordinarily encounter during routine physical or psychological examinations or standard of care procedures to treat their medical condition, the exemption request would have to include information to demonstrate that the procedures do not present a potential for significant risk to the health, safety, or welfare of these subjects (proposed § 312.2(b)(5)(i)(F)(4));

- If the proposed conditions of use of the product in the investigation differ from the product's labeled or ordinary conditions of use, the exemption request would have to include an explanation of why the proposed conditions of use do not present a potential for significant risk to the health, safety, or welfare of the subjects (proposed § 312.2(b)(5)(i)(F)(5)); and
  - If the investigational product is being used concurrently with other products that a subject is taking or being treated with, either as part of the study or as prescribed or recommended by a healthcare provider outside the study, the exemption request would have to include information to demonstrate that the investigational product has a history of safe use with those products or is otherwise not expected to have clinically significant interactions with the other products (proposed § 312.2(b)(5)(i)(F)(6)).
- g. Other information as requested by FDA.

A request for exemption would have to include any other information requested by FDA for use in reviewing the exemption request (proposed § 312.2(b)(5)(i)(G)). This means that the sponsor would have to provide additional information if, upon reviewing the request, we found that such information was necessary to determine whether the investigation met the exemption criteria. For example, if a sponsor provided insufficient information to explain why use of the investigational product in a manner that differs from its labeled conditions of use did not present a potential for significant risk to subjects, we would ask for additional information to address concerns about the different conditions of use.

## 2. Submitting a Request for Exemption

A sponsor seeking an FDA-determined exemption would have to submit a written request to CBER or CDER at the appropriate address set forth in § 312.140(a), which specifies where to send a new IND for a drug or biological product (proposed § 312.2(b)(5)(ii)). Sponsors should consult the 2013 IND Guidance (or successor guidance) to find the appropriate contact for inquiries about when the IND requirements apply (see Ref. 1). The FDA components listed in

the guidance may also be consulted for help in determining the appropriate Center to which an exemption request should be submitted.

### 3. FDA Action on a Request for Exemption

Upon receiving a complete exemption request, FDA would evaluate any risks to subjects that may result from participation in the clinical investigation (proposed § 312.2(b)(5)(iii)). We would grant an exemption from the IND regulations if we found that the investigation satisfied the requirements of § 312.2(b)(4)(i) through (iv) and did not present a potential for significant risk to the health, safety, or welfare of the subjects. We would notify the sponsor in writing whether the request for an FDA-determined exemption was granted. An exemption granted under this provision would not become effective until the sponsor received written notification that we had granted the exemption.

### 4. FDA-Initiated Exemption

In addition to permitting FDA to grant an exemption following the request of a sponsor, the proposed rule would allow FDA to exempt a study from the IND requirements if we determine, after reviewing an IND for a study, that the study meets the decision criteria for an FDA-determined exemption (i.e., the study meets the requirements in proposed § 312.2(b)(4)(i) through (iv) and the study does not present a potential for significant risk to the health, safety, or welfare of subjects). We believe there might be instances in which, although a sponsor had submitted an IND for a study and had not requested an exemption, we might conclude, upon reviewing the IND, that the study meets the decision criteria for an FDA-determined exemption. (We also might conclude that a study for which an IND has been submitted meets all the criteria for a self-determined exemption. If so, we would simply refuse to accept the IND under § 312.2(b)(4) (redesignated in the proposed rule as § 312.2(b)(6)), as we do when we receive an IND for a study of a lawfully marketed drug product that meets the exemption criteria in § 312.2(b)(1).) Exempting on our own initiative a study that meets the criteria for an FDA-determined exemption would reduce the regulatory burden on both the sponsor and FDA without

causing harm to the health, safety, or welfare of study subjects. Therefore, proposed § 312.2(b)(5)(iv) provides that FDA may grant an exemption from the IND requirements on our own initiative after reviewing an IND and determining that the clinical investigation for which the IND was submitted satisfies the requirements of § 312.2(b)(4)(i) through (iv) and does not present a potential for significant risk to the health, safety, or welfare of subjects. Proposed § 312.2(b)(5)(iv) further states that if FDA decides to grant an exemption under § 312.2(b)(5)(iv), we will notify the sponsor or sponsor-investigator of the exemption in writing, and that the exemption will become effective when the sponsor or sponsor-investigator receives written notification that we have granted the exemption.

#### 5. Revocation of an FDA-Determined Exemption

Under proposed § 312.2(b)(5)(v), we could revoke a previously granted exemption (whether requested by a sponsor under proposed § 312.2(b)(5)(i) or initiated by FDA under proposed § 312.2(b)(5)(iv)) if we become aware of information suggesting that the clinical investigation presents a potential for significant risk to the health, safety, or welfare of study subjects, or that the investigation does not meet any other requirement for the FDA-determined exemption (such as the requirement that the route of administration of the product in the investigation be the same as that of the lawfully marketed product). For example, we might revoke an exemption if we learn that subjects are experiencing clinically significant adverse events associated with the investigational product or if we learn of an interaction between the investigational product and another product prescribed for or dispensed to study subjects. If we learn of something that creates a potential for significant risk to subjects, we may conclude that the study must be conducted in accordance with the IND requirements to provide adequate protection to subjects. If we decided to revoke an exemption, we would notify the sponsor of the reason for revoking the exemption and, if appropriate, direct the sponsor to suspend the investigation and/or cease recruiting new subjects to the investigation.

#### *C. Proposed Technical and Conforming Amendments*

In accordance with the proposed addition of the self-determined exemption in § 312.2(b)(4) and the FDA-determined exemptions in § 312.2(b)(5), we propose to renumber the existing provisions in § 312.2(b)(4) through (b)(6) as § 312.2(b)(6) through (b)(8).

We also propose to make a conforming amendment to existing § 312.2(b)(4) (to be renumbered as § 312.2(b)(6)), which states that FDA will not accept an application (IND) for an investigation that is exempt from the IND requirements under § 312.2(b)(1). We propose to include investigations exempted under the self-determined and FDA-determined exemption provisions among those for which we will not accept an IND.

## VI. Proposed Effective Date

We propose that any final rule resulting from this rulemaking become effective 30 days after the date of its publication in the *Federal Register*.

## VII. Preliminary Economic Analysis of Impacts

### A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule would create net cost savings for the affected industry by reducing the number of INDs that must be submitted to FDA, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

### *B. Summary of Costs and Benefits*

Quantifiable benefits of this proposed rule are cost savings that come from reducing the burden of submitting INDs to FDA for clinical investigations evaluating drug uses of foods for human consumption (including dietary supplements) and cosmetics. The cost savings go to sponsors and sponsor-investigators (collectively, “sponsors”), typically physicians and other researchers at hospitals and academic institutions, who would no longer need to submit as many INDs because the proposed rule provides exemptions for qualifying drug studies of products lawfully marketed as a food or cosmetic. The proposed rule would also provide cost savings to FDA, which would not need to evaluate and monitor as many INDs. We expect the average present value of the benefits to be \$28 million at a 7 percent discount rate and \$34 million at a 3 percent discount rate over a 10-year time horizon.

If this proposed rule is finalized, sponsors would incur a one-time cost because they, or lawyers or consultants acting on their behalf, would have to spend time reading the rule to understand what studies are eligible for exemption and how to request an FDA-determined exemption. We estimate that 557 sponsors would read the rule the first year and 279 additional sponsors would read the rule in subsequent years. We estimate the cost of reading the rule to be \$153 per sponsor. We expect the average present value of the reading cost to be \$418,000 at a 3 percent discount rate and \$364,000 at a 7 percent discount rate over a 10-year time horizon. In

addition, there would be costs to FDA associated with a new type of IND-related submission, a request for an FDA-determined exemption. We have analyzed this cost as a partial offset to the cost savings of the rule. The total net benefit of the rule is estimated to be \$33 million at a 3 percent discount rate and \$27 million at a 7 percent discount rate.

Table 1 provides annualized values for the estimated benefits and costs of the proposed rule:

Table 1.--Summary of Benefits, Costs and Distributional Effects of Proposed Rule

| Category  |  | Primary Estimate | Low Estimate | High Estimate | Units        |               |                | Notes                            |
|-----------|--|------------------|--------------|---------------|--------------|---------------|----------------|----------------------------------|
|           |  |                  |              |               | Year Dollars | Discount Rate | Period Covered |                                  |
| Benefits  | Annualized Monetized \$/year   | \$3,450,000      | (\$850,000)  | \$7,730,000   | 2021         | 7%            | 10             | Cost savings to FDA and industry |
|           |  | \$3,530,000      | (\$780,000)  | \$7,840,000   | 2021         | 3%            | 10             |                                  |
|           | Annualized Quantified  |                  |              |               |              | 7%            |                |                                  |
|           |  |                  |              |               |              | 3%            |                |                                  |
|           | Qualitative  |                  |              |               |              |               |                |                                  |
| Costs     | Annualized Monetized \$/year   | \$45,300         | \$15,700     | \$77,800      | 2021         | 7%            | 10             |                                  |
|           |  | \$43,800         | \$15,100     | \$75,700      | 2021         | 3%            | 10             |                                  |
|           | Annualized Quantified  |                  |              |               |              | 7%            |                |                                  |
|           |  |                  |              |               |              | 3%            |                |                                  |
|           | Qualitative  |                  |              |               |              |               |                |                                  |
| Transfers | Federal Annualized Monetized \$/year                                       |                  |              |               |              | 7%            |                |                                  |
|           |  |                  |              |               |              | 3%            |                |                                  |
|           | From/ To   | From:            |              |               | To:          |               |                |                                  |
|           | Other Annualized Monetized \$/year   |                  |              |               |              | 7%            |                |                                  |
|           |  |                  |              |               |              | 3%            |                |                                  |
|           | From/To  | From:            |              |               | To:          |               |                |                                  |
| Effects   | State, Local or Tribal Government:<br>Small Business:<br>Wages:<br>Growth: |                  |              |               |              |               |                |                                  |

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. This full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 3) and at <https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations>.

## VIII. Analysis of Environmental Impact



We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### IX. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). This analysis provides a description of these provisions and an estimate of the annual reporting burden associated with the proposed rule. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

*Title:* Exemptions from IND Requirements for Certain Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Food (Including a Dietary Supplement) or Cosmetic (Revision to Investigational New Drug (IND) Regulations--OMB Control Number 0910-0014).

*Description:* The proposed rule would revise FDA's IND regulations to exempt from the IND requirements certain clinical investigations of foods for human consumption (including dietary supplements) or cosmetics. For one type of proposed exemption, respondents must submit a written request to FDA electronically or in paper form.

*Description of Respondents:* Respondents to the information collection are individuals and organizations who plan to conduct or sponsor a clinical investigation evaluating a drug use of a product lawfully marketed in the United States as a conventional food, dietary supplement, or cosmetic for human use.

The reporting and recordkeeping requirements in part 312 provide the means by which FDA can monitor clinical investigations of the safety and effectiveness of unapproved new drugs and biological products. Information provided by applicants (sponsors and sponsor-investigators) allows us to monitor the safety of ongoing clinical investigations as well as help ensure the reliability and quality of data submitted in support of drug marketing applications. While the regulations provide an exemption from most IND requirements for studies of lawfully marketed drug products that meet certain criteria, including that the study does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks associated with the use of the drug product (see § 312.2(b)(1)), the proposed rule would codify IND exemptions for clinical studies investigating drug uses of lawfully marketed foods for human consumption or cosmetics.

We estimate the burden of the information collection for the proposed rule as follows:

Table 2.--Estimated Annual Reporting Burden<sup>1</sup>

| 21 CFR Part                                | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|--|--------------------|---------------------------------|------------------------|-----------------------------|-------------|
| 312.2(b)(5); Written request for exemption | 28                 | 1                               | 28                     | 24                          | 672         |

<sup>1</sup> There are no capital costs or operating and maintenance costs associated with this collection of information.

The proposed rule would create two types of IND exemptions for clinical investigations to evaluate drug uses of products lawfully marketed for human use in the United States as conventional foods, dietary supplements, or cosmetics. Under proposed § 312.2(b)(4) and (5), respondents could qualify for, respectively, either a “self-determined exemption” or an “FDA-determined exemption” from the IND requirements, provided certain criteria were met. Under the self-determined exemption, if an investigation met the requirements for the exemption, the

sponsor or sponsor-investigator would not have to submit an IND for the study or request that FDA exempt the study from the IND requirements. To obtain an FDA-determined exemption, a sponsor or sponsor-investigator would submit a written request for exemption that includes a copy of the study protocol or a detailed protocol summary with information about the study design, investigational product, and procedures; the names of the manufacturer and source of the product to be studied; the name (if different from the name of the product to be studied in the investigation) and form of the lawfully marketed food or cosmetic product, accompanied by a copy of the product's labeling and, if the labeling does not list the product's ingredients, a description of the product's composition; the source(s) of funding for the investigation; the name, address, telephone number, email address, and contact name for the sponsor or sponsor-investigator; a brief description of why the investigation does not present a potential for significant risk to the health, safety, or welfare of subjects; and any other information requested by FDA.<sup>1</sup>

As shown in table 2, we estimate that 28 total sponsors and sponsor-investigators will submit requests for exemption annually and that preparing a request will take approximately 24 hours. The Preliminary Economic Analysis of Impacts for the proposed rule (Ref. 3) estimates that, of the 322 clinical investigations of foods (including dietary supplements) or cosmetics that were the subject of INDs or IND-related inquiries received between 2016 and 2020, we likely would have granted an FDA-determined exemption for 68 studies (approximately 14 each year) had the proposed rule been in effect and the exemption requests been submitted. Because we believe that codifying the FDA-determined exemption in the regulations would make sponsors and sponsor-investigators more likely to seek an exemption, we have doubled the figure of 14 investigations, resulting in an estimated 28 requests for an FDA-determined exemption each

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<sup>1</sup> The proposed rule also would authorize FDA to grant an exemption from the IND requirements on our own initiative when we determined, upon review of an IND for a study, that the study met the decision criteria for an FDA-determined exemption. However, as with the self-determined exemption, this FDA-initiated exemption would not impose any burden on sponsors or sponsor-investigators.

year. The estimated time for preparation of a request, 24 hours, is based on the time needed to assemble the information required to be included in the request and describe why the investigation does not present a potential for significant risk to the health, safety, and welfare of subjects. We believe this burden is comparable to the burden associated with preparing a request for advice on whether the IND requirements apply to a planned clinical investigation under § 312.2(e), which we have estimated to be 24 hours (84 FR 3462 at 3463, February 12, 2019). However, we invite comment on the accuracy of this estimate.

Although the proposed procedure for requesting an FDA-determined exemption would create a new reporting element for exemption requests, the proposed rule would likely also reduce burden associated with requesting FDA advice on the applicability of the IND regulations to particular clinical investigations under § 312.2(e). Amending the IND regulations to exempt certain clinical investigations of foods and cosmetics would reduce the need for consulting FDA in this regard because sponsors and sponsor-investigators who use one of the new exemption pathways would not need to use the § 312.2(e) mechanism to ask FDA's advice on whether an IND is required for their clinical investigations to evaluate a drug use of such products.

To ensure that comments on this information collection are received, OMB recommends that written comments be through [reginfo.gov](https://www.reginfo.gov) (see ADDRESSES). All comments should be identified with the title of the information collection.

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3407(d)), we have submitted the information collection provisions of this proposed rule to OMB for review. These information collection requirements will not be effective until FDA publishes a final rule, OMB approves the information collection requirements, and the rule goes into effect. FDA will announce OMB approval of these requirements in the *Federal Register*.

## X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies

that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the proposed rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

#### XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the proposed rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. We invite comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

#### XII. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <https://www.regulations.gov>. FDA has verified the website addresses as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA, “Guidance for Clinical Investigators, Sponsors, and Institutional Review Boards (IRBs) on Investigational New Drug Applications--Determining Whether Human Research Studies Can Be Conducted Without an IND”, available at <https://www.fda.gov/media/79386/download>.

2. FDA Consumer Update, “Avoiding Drug Interactions”, available at <https://www.fda.gov/consumers/consumer-updates/avoiding-drug-interactions>.

3. FDA, Preliminary Economic Analysis of Impacts, Docket No. FDA-2019-N-2650, available at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

### **List of Subjects in 21 CFR Part 312**

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 312 be amended as follows:

### **PART 312--INVESTIGATIONAL NEW DRUG APPLICATION**

1. The authority citation for part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360bbb, 371; 42 U.S.C. 262.

2. Amend § 312.2 by:

- a. Redesignating paragraphs (b)(4) through (6) as paragraphs (b)(6) through (8);
- b. Revising newly redesignated paragraph (b)(6); and
- c. Adding new paragraphs (b)(4) and (5).

The revision and additions read as follows:

#### **§ 312.2 Applicability.**

\* \* \* \* \*

(b) \* \* \*

(4) A clinical investigation to evaluate a drug use of a product that is lawfully marketed in the United States as a food intended for human consumption (including as a conventional food or dietary supplement) or as a cosmetic, is exempt from the requirements of this part if all of the following apply:

- (i) The investigation is not intended to support:

(A) A drug development plan for the product, including a future IND or application for marketing approval (an application under section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act); or

(B) A change in the labeling of the lawfully marketed product that would cause it to become an unlawfully marketed drug;

(ii) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 of this title and the requirements for informed consent set forth in part 50 of this title;

(iii) The investigation is conducted in compliance with the requirements of § 312.7;

(iv) The route of administration of the product in the investigation is the same as that of the lawfully marketed product; and

(v) The investigation meets all of the following criteria:

(A) The investigation does not include subjects who are less than 12 months of age or subjects who are pregnant or lactating;

(B) The investigation does not include subjects with a compromised immune system or a serious or life-threatening disease or condition;

(C) The investigation does not restrict subjects from continuing with treatments or therapies prescribed or recommended by a healthcare provider;

(D) The investigation does not involve any procedures that would increase the risks (or decrease the acceptability of the risks) to subjects beyond what they would ordinarily encounter during routine physical or psychological examinations or standard of care procedures to treat their medical condition;

(E) The product is being used in the investigation consistent with its labeled conditions of use when lawfully marketed as a food or cosmetic or, in the absence of labeled conditions of use, consistent with its ordinary conditions of use as a lawfully marketed food or cosmetic (e.g., same dose range and total daily intake, same formulation, same duration of use); and

(F) During the investigation, subjects are not taking and will not be treated with any other product(s) that would significantly increase the risks (or decrease the acceptability of the risks) they will encounter in the investigation (e.g., from drug interactions).

(5)(i) A sponsor or sponsor-investigator may request that FDA exempt from the requirements of this part a clinical investigation to evaluate a drug use of a product that is lawfully marketed in the United States as a food intended for human consumption (including as a conventional food or dietary supplement) or as a cosmetic, when the investigation satisfies the requirements of paragraphs (b)(4)(i) through (iv) of this section, but not paragraph (b)(4)(v) of this section, and the sponsor or sponsor-investigator has concluded that the investigation does not present a potential for significant risk to the health, safety, or welfare of subjects. Such requests must be made in writing and must contain the following:

(A) A copy of the study protocol or protocol summary that includes, at a minimum, the following:

- (1) Study design;
- (2) Proposed endpoints;
- (3) Study population, including inclusion and exclusion criteria for subjects;
- (4) Duration of the study;
- (5) Description of the product to be studied as an investigational drug, including ingredients, composition, and any labeling;
- (6) Dosage form, dosing regimen, and route of administration of the investigational drug;
- (7) Study procedures (including safety monitoring procedures); and
- (8) Planned modifications to the protocol in the event of adverse events.

(B) The names of the manufacturer and of the entity that is the source of the product to be studied in the investigation. For foods not in package form and not labeled with the name of the manufacturer, only the source of the product is required;



(C) The name (if different from the name of the product to be studied in the investigation) and form of the lawfully marketed food or cosmetic product; a copy of the product labeling; and, if the labeling does not identify the ingredients of the lawfully marketed product, a description of the product's composition;

(D) The source(s) of funding for the investigation;

(E) The name, address, telephone number, email address, and contact name for the sponsor or sponsor-investigator;

(F) A brief description of why the investigation does not present a potential for significant risk to the health, safety, or welfare of subjects, including, where relevant, the following information to justify an exemption:

(1) If the investigation includes subjects who are less than 12 months of age or subjects who are pregnant or lactating, information to demonstrate that the use of the product in the investigation does not present a potential for significant risk to the health, safety, or welfare of these subjects;

(2) If the investigation includes subjects with a compromised immune system or a serious or life-threatening disease or condition, information to demonstrate that the use of the product in the investigation does not present a potential for significant risk to the health, safety, or welfare of these subjects;

(3) If participation in the investigation will preclude subjects from continuing with a treatment or therapy prescribed or recommended for them by a healthcare provider (e.g., if some subjects are randomized to the investigational product or placebo instead of their current treatment), an explanation of why this restriction does not present a potential for significant risk to the health, safety, or welfare of these subjects;

(4) If the subjects in the investigation will undergo any procedures during the investigation that would expose them to more risk than they would ordinarily encounter during routine physical or psychological examinations or standard of care procedures to treat their

medical condition, information to demonstrate that the procedures do not present a potential for significant risk to the health, safety, or welfare of these subjects;

(5) If the proposed conditions of use of the product in the investigation differ from the product's labeled or ordinary conditions of use, an explanation of why the proposed conditions of use do not present a potential for significant risk to the health, safety, or welfare of the subjects; and

(6) If the investigational product is being used concurrently with other products that the subject is taking or being treated with as part of the study or for other reasons as prescribed or recommended by a healthcare provider, information to demonstrate that the investigational product has a history of safe use with those products or is otherwise not expected to have clinically significant interactions with the other products; and

(G) Any other information requested by FDA for use in reviewing the exemption request.

(ii) A sponsor or sponsor-investigator requesting an exemption under paragraph (b)(5)(i) of this section must submit the request to the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research at the appropriate address set forth in § 312.140(a).

(iii) Upon receiving an exemption request under paragraph (b)(5)(i) of this section, FDA will evaluate any risks to subjects that may result from participation in the clinical investigation and will grant an exemption from the requirements of this part if we find that the investigation satisfies the requirements of paragraphs (b)(4)(i) through (iv) of this section and does not present a potential for significant risk to the health, safety, or welfare of the subjects. FDA will notify the sponsor or sponsor-investigator in writing whether the request for exemption is granted. An exemption will become effective when the sponsor or sponsor-investigator receives written notification that we have granted the exemption.

(iv) FDA may grant an exemption from the requirements of this part on our own initiative after reviewing an IND and determining that the clinical investigation for which the IND was

submitted satisfies the requirements of paragraphs (b)(4)(i) through (iv) of this section and does not present a potential for significant risk to the health, safety, or welfare of the subjects. If FDA grants such an exemption, we will notify the sponsor or sponsor-investigator of the exemption in writing. The exemption will become effective when the sponsor or sponsor-investigator receives written notification that we have granted the exemption.

(v) FDA may revoke an exemption granted under paragraph (b)(5)(iii) or (iv) of this section if we become aware of information suggesting that the clinical investigation could present a potential for significant risk to the health, safety, or welfare of subjects, or that the investigation does not meet any requirement in paragraphs (b)(4)(i) through (iv) of this section. FDA will notify the sponsor or sponsor-investigator who received the exemption of the reason for revoking the exemption and, if appropriate, may direct the sponsor or sponsor-investigator to suspend the investigation and/or cease recruiting new subjects to the investigation.

(6) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1), (b)(4), or (b)(5) of this section.

\* \* \* \* \*

Dated: November 28, 2022.

**Robert M. Califf,**

*Commissioner of Food and Drugs.*

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